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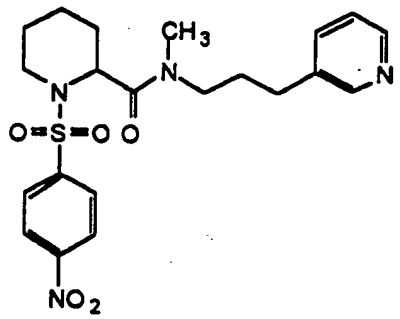
(54) Title: COMPOUNDS POSSESSING NEURONAL ACTIVITY

(57) Abstract

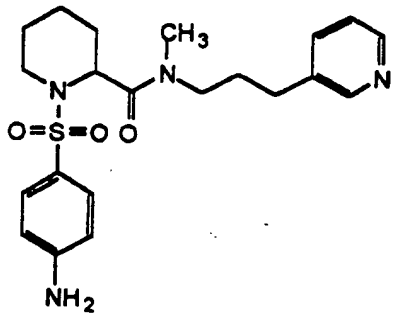
The present invention relates to compounds, methods and pharmaceutical compositions for stimulating the growth of neurites in nerve cells. The compounds and the compositions and methods that utilize them can be used, either alone or in conjunction with a neurotrophic factor, such as nerve growth factor, to promote repair of neuronal damage caused by disease or physical trauma.

E. N-(4-nitrobenzenesulfonamido)-(S)-piperidine-2-carboxylic acid-((N-methyl)-3-(pyridin-3-yl)propyl) amide.



To a solution of the compound from step D (250 mg; 0.96 mmol) in methylene chloride (15 ml) was added triethylamine (2.0 ml, 101.19, 19.8 mmol) followed by the addition of 4-nitrobenzenesulfonylchloride (300 mg, 1.42 mmol). The mixture was allowed to stir at ambient temperature for 24 hours. The solution was diluted with 200 ml ethyl acetate and a saturated solution of sodium bicarbonate (50 ml). The separated organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via medium pressure liquid chromatography using a gradient solvent system of methylene chloride followed by 1:99 methanol/ methylene chloride solution to give 165 mg (37% yield) of the title compound as a yellowish oil. TLC: Rf=0.52 (5:95 methanol/ methylene chloride), [^{1}H]-NMR ($CDCl_3$) consistent with structure.

F. N-(4-nitrobenzenesulfonamido)-(S)-piperidine-2-carboxylic acid-((N-methyl)-3-(pyridin-3-yl)propyl) amide (compound 3).



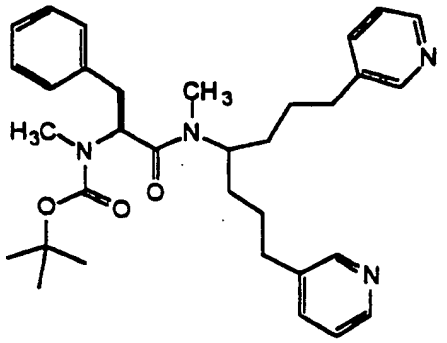
A solution of the compound from step E (165 mg, 0.35 mmol) in ethyl acetate (20 ml) was treated under ambient temperature with 150 mg of 10% palladium on carbon and hydrogenated for 24 hours under a slight positive pressure of hydrogen. The mixture was filtered and concentrated in vacuo and the crude product purified via medium pressure liquid chromatography using methylene chloride followed by 2:98 methanol/ methylene chloride followed by 0.5:5:95 NH_4OH/methanol/ methylene chloride solution as the solvent system to give 60 mg (41% yield) of the title compound as a yellowish oil. TLC: Rf=0.20 (5:95 methanol/methylene chloride), HPLC: Rt= 7.25 min, [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 4

(S)-(N-Methyl)-2-(Methyl-(4-Amino-Benzenesulfanilamido))-3-Phenyl-N-(4-(Pyridin-3-Yl)-1-(3-(Pyridin-3yl)Propyl) Butyl) propionamide

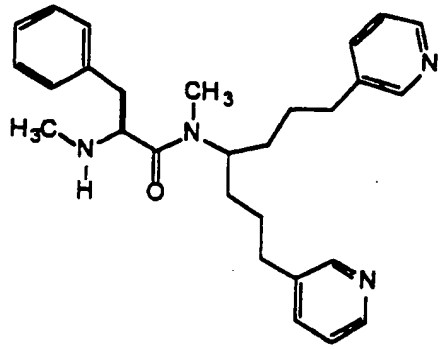
The synthesis of (S)-(N-methyl)-2-(methyl-(4-amino-benzenesulfanilamido))-3-phenyl-N-(4-(pyridin-3-yl)-1-(3-(pyridin-3yl)Propyl) butyl) propionamide is set forth below.

A. (S)-(N-methyl)-2-(methyl-2-tertbutyloxycarbonyl)amino)-3-phenyl-N-(4-(pyridin-3-yl)-1-(3-(pyridin-3-yl)propyl)butyl) propionamide.



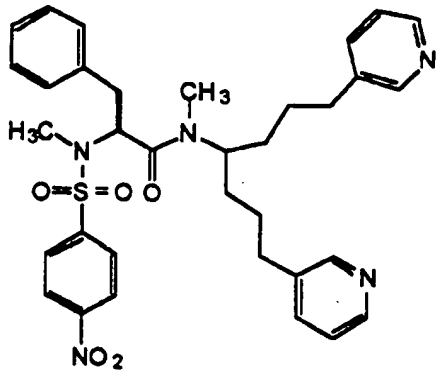
To a solution of Boc-(N-Methyl)phenylalanine (1.42 g, 5.1 mmol) in methylene chloride (10 ml) was added EDC (0.98 g, 191.71, 5.1 mmol) followed by the addition of N-methyl-1,7 bis(3-pyridyl)-4-heptylamine (1.2 g, 18.4 mmol). The mixture was allowed to stir at ambient temperature for 24 hours. The solution was diluted with 100 ml ethyl acetate and a saturated solution of sodium bicarbonate (50 ml). The separated organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via medium pressure liquid chromatography using 2:98 methanol/methylene chloride solution to give 970 mg (42% yield) of the title compound as a colorless oil. TLC: Rf=0.51 (5:95 methanol/ methylene chloride), [^{1}H]-NMR ($CDCl_3$) consistent with structure.

B. (S)-(N-methyl)-2-(methylamino)-3-phenyl-N-(3-(pyridin-4-yl)-1-(4-(pyridin-3yl)propyl)butyl) propionamide.



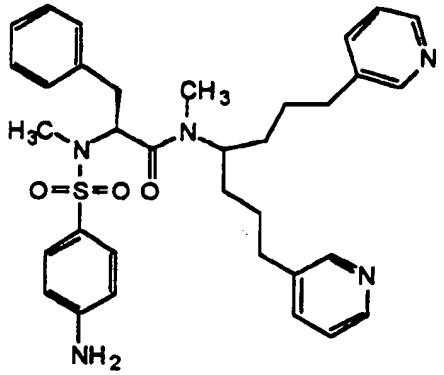
To the compound of step A (5.0 g, 9.2 mmol) in methylene chloride (20 ml) was added trifluoroacetic acid (20 ml, 260 mmol). The mixture was allowed to stir 3 hours at ambient temperature. The solution was concentrated under reduced pressure to dryness. The residue was taken up in ethyl acetate (200 ml) and a saturated solution of sodium bicarbonate (100 ml). The separated organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via medium pressure liquid chromatography using a gradient solvent system of 1:99 methanol/ methylene chloride followed by 5:95 methanol/ methylene chloride followed by 1:10:90 NH_4OH/methanol/methylene chloride) to give 3.12 g (76% yield) of the title compound as a colorless oil. TLC: Rf=0.38 (1:10:90 NH_4OH/methanol/methylene chloride). HPLC: Rt= 9.52 min, [^{1}H]-NMR ($CDCl_3$) consistent with structure.

C. (S)-(N-methyl)-2-(methyl-(4-nitrobenzenesulfanilamido))-3-phenyl-N-(4-(pyridin-3-yl)-1-(3-(pyridin-3-yl)propyl)Butyl) propionamide.



To a solution of the compound of step B (1.5 g, 3.4 mmol) in methylene chloride (20 ml) was added triethylamine (5.0 ml, 101.19, 35.8 mmol) followed by the addition of 4-nitrobenzenesulfonylchloride (1.0 g, 4.7 mmol). The mixture was allowed to stir at ambient temperature for 24 hours. The solution was diluted with 150 ml ethyl acetate and washed with water (50 ml). The separated organics were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified via medium pressure liquid chromatography using a gradient solvent system of methylene chloride followed by 1:99 methanol/methylene chloride solution to give 1.75 g (83% yield) of the title compound as a yellowish oil. TLC: Rf=0.67 (5:95 methanol/methylene chloride), [^{1}H]-NMR ($CDCl_3$) consistent with structure.

D. (S)-(N-methyl)-2-(methyl-(4-amino-benzenesulfanilamido))-3-phenyl-N-(4-(pyridin-3-yl)-1-(3-(pyridin-3-yl)propyl)butyl) propionamide (compound 4).



A solution of the compound of step C (1.75 g, 2.78 mmol) in ethyl acetate (50 ml) was treated under ambient temperature with 1.0 g of 10% palladium on carbon and hydrogenated for 24 hours under a slight positive pressure of hydrogen. The mixture was filtered and concentrated in vacuo and the crude product purified via medium pressure liquid chromatography using methylene chloride followed by 1:99 methanol/methylene chloride followed by 3:97 methanol/methylene chloride solution as the solvent system to give 0.79 mg (47% yield) of the title compound as a yellowish oil. TLC: Rf=0.36 (1:10:90 NH_4OH/methanol/ methylene chloride). HPLC: Rt= 7.97 min, [^{1}H]-NMR ($CDCl_3$) consistent with structure.

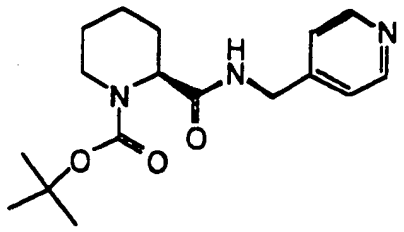
The synthesis of other compounds of this invention, including those listed in Table 1 above, may be achieved by modifying the synthesis schemes set forth in Examples 1-4 using appropriate reagents that are well known in the art.

EXAMPLE 5

(S)-Piperidine-2-Carboxylic Acid, (4-Pyridylmethyl) Amide, Citrate Salt

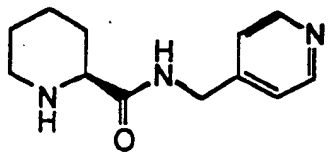
The synthesis of (S)-piperidine-2-carboxylic acid-1-(tert-butyl ester)-2-(4-pyridylmethyl) amide, citrate salt (compound 1) is set forth below.

A. (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester)-2-(4-pyridylmethyl) amide



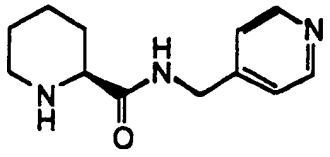
Following the method described in Example 1, part A, (S)-piperidine-1,2 dicarboxylic acid-1-(tert-butyl ester) (2.0 g, 8.72 mmol) and 4-(aminomethyl) pyridine (3.18 g, 29.41 mmol) was converted to 0.75 g (27% yield) of product. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

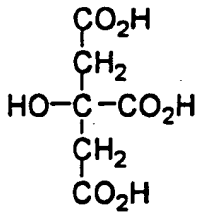
B. (S)-Piperidine-2-Carboxylic acid, (4-Pyridylmethyl) Amide



Following the method of Example 1, part B, (S)-piperidine-1-carboxylic acid-1-(tert-butyl ester)-2-(4-pyridylmethyl) amide (0.75 g, 2.35 mmol) gave 0.49 g (95% yield) of the title compound. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

C. (S)-Piperidine-2-Carboxylic acid, (4-Pyridylmethyl) Amide, Citrate Salt





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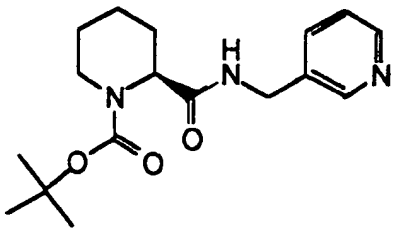
A solution of the amine (107 mg, 0.48 mmol) from part B and citric acid (94 mg, 0.48 mmol) in absolute ethanol was warmed to 60°C until dissolved. The solution was concentrated in vacuo and the residue was dissolved in absolute ethanol and concentrated in vacuo to give a foam. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 6

(S)-Piperidine-2-Carboxylic Acid, (4-Pyridylmethyl) Amide, Citrate Salt

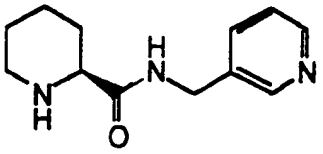
The synthesis of (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester)-2-(3-pyridylmethyl) amide, citrate salt is set forth below.

A. (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester)-2-(3-pyridylmethyl) amide



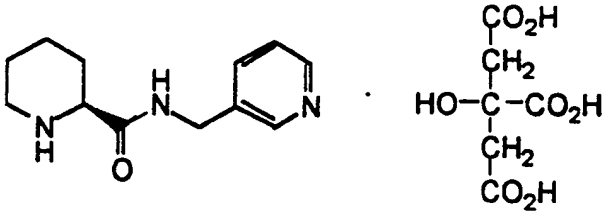
Following the method described in Example 1, part A, (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester) (2.0 g, 8.72 mmol) and 3-(aminomethyl) pyridine (3.18 g, 29.41 mmol) was converted to 1.0 g (36% yield) of product. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

B. (S)-Piperidine-2-Carboxylic acid, (3-Pyridylmethyl) Amide



Following the method of Example 1, part B, (S)-piperidine-1,2-dicarboxylic acid-1-(tert-butyl ester)-2-(3-pyridylmethyl) amide (1.0 g, 3.13 mmol) gave 0.56 g (82% yield) of the title compound. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

C. (S)-Piperidine-2-Carboxylic acid, (2-Pyridylmethyl) Amide, Citrate Salt



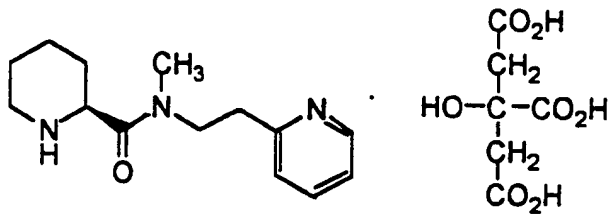
103

A solution of the amine (111 mg, 0.51 mmol) in part B and citric acid (97 mg, 0.51 mmol) was warmed to 60°C until dissolved. The solution was concentrated in vacuo and the residue was dissolved in absolute ethanol and concentrated in vacuo to give a foam. [^{1}H]-NMR ($CDCl_3$)

consistent with structure.

EXAMPLE 7

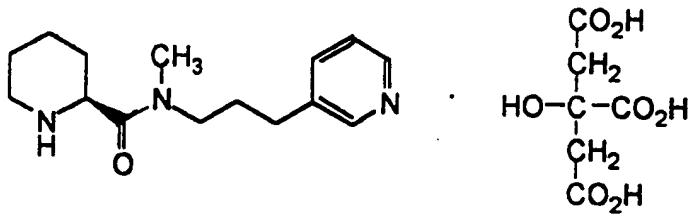
(S)-Piperidine-2-Carboxylic Acid-2-((N Methyl)-2-Pyridylethyl) Amide, Citrate Salt



Following the method described in Example 5, part C, (S)-piperidine-2-carboxylic acid-2-((N methyl)-2-pyridylethyl) amide (product in example 1, part B) was converted to a citrate salt. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 8

(S)-Piperidine-2-Carboxylic acid-((N-Methyl)-3-(Pyridin-3-yl)Propyl) Amide, Citrate Salt

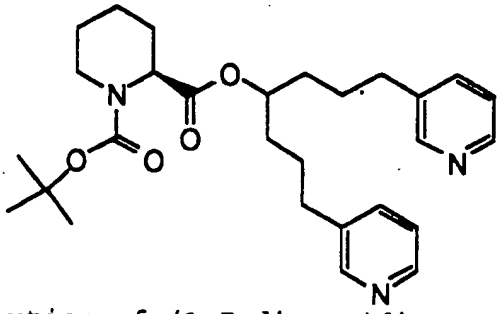


Following the procedure described in Example 6, part C, S)-piperidine-2-carboxylic acid-((N-methyl)-3-(pyridin-3-yl)propyl) amide (product from Example 3, part D) was converted to a citrate salt. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 9

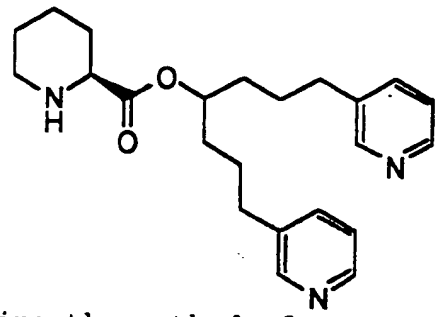
(S)-Piperidine-2-Carboxylic Acid, (1,7-di-pyridin-3-yl)heptan-4-yl) ester, Fumarate Salt

A. (S)-Piperidine-1,2-Dicarboxylic Acid-1-(Tert-Butyl ester)-2-(1,7-di-pyridin-3-yl)heptan4-yl) ester



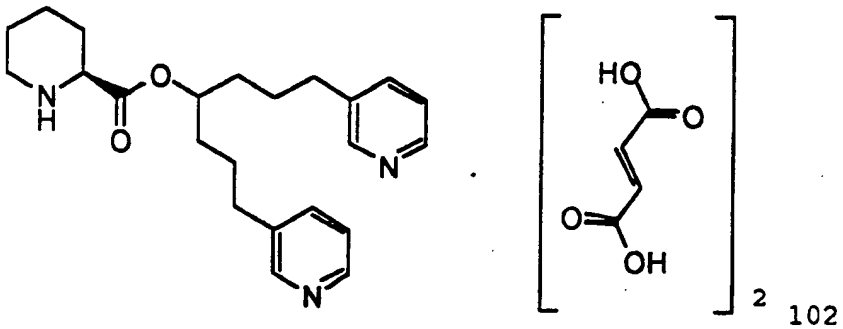
A solution of (1,7-di-pyridin-3-yl)heptan-4-ol (6.6 g, 24.41 mmol) in THF (30 ml) was added to (S)-piperidine-1,2 dicarboxylic acid-1-(tert-butyl ester) (5.0 g, 21.81 mmol) and EDC (4.7 g, 24.52 mmol) and allowed to stir for 18 h at room temperature. The reaction was diluted with ethyl acetate (200 ml) and washed with water. The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by medium pressure liquid chromatography using 1:100 methanol/methylene chloride as the solvent system to give 2.0 g (20% yield) of the title compound. [^1H]-NMR ($CDCl_3$) consistent with structure.

B. (S)-Piperidine-2-Carboxylic Acid, (1,7-di-pyridin-3-yl)heptan-4-yl) ester



Following the method of Example 1, part B, the compound from Example 10, part A, (1.0 g, 4.30 mmol) gave 1.45 g (88% yield) of the title compound. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

C. (S)-Piperidine-2-Carboxylic Acid, (1,7-di-pyridin-3-yl)heptan-4-yl) ester, Bis-fumarate Salt



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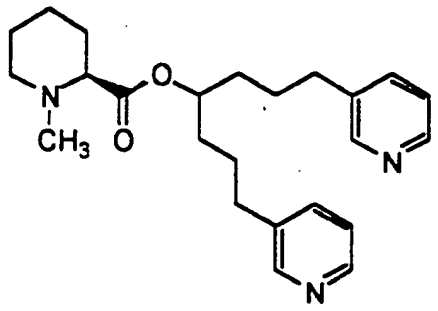
Following the procedure in Example 6, part C, the amine in example 10, part C may be converted to the title compound using 1 equivalent of the amine and two equivalents of fumaric acid. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 10

(S)-1-Methyl-Piperidine-2-Carboxylic Acid, (1,7-di-pyridin-3-yl)heptan-4-yl) ester

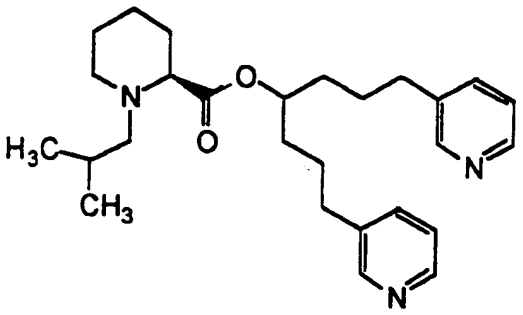


111

A mixture of the amine (300 mg, 0.79 mmol) from Example 10, part B and paraformaldehyde (500 mg) in methanol (15 ml) was added to $Na(CN)BH_3$ (500 mg). The mixture was stirred for 65 h at room temperature. The reaction was concentrated in vacuo and taken up in 2N aqueous NaOH and extracted with ethyl acetate (150ml). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by medium pressure liquid chromatography using a gradient solvent system of 2:98 methanol/methylene chloride followed by 0.5:5:95 NH_4OH/methanol/methylene chloride to give 230 mg (74% yield) of the title compound as a clear oil. [^1H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 11

(S)-1-(2-Methylpropyl)-Piperidine-2-Carboxylic Acid, (1,7-di-pyridin-3-yl)heptan-4-yl) ester



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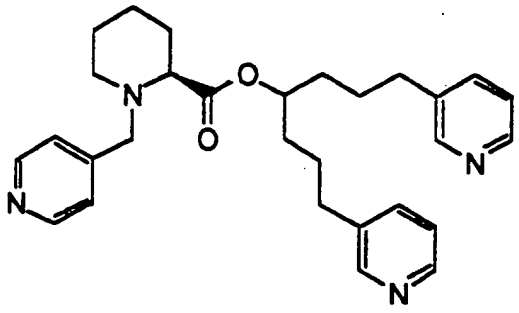
Following the method described in Example 11, mixture of the amine (300 mg, 0.79 mmol) from Example 10, part B and 2-methylpropionaldehyde (1.6 g, 22.0 mmol) in methanol (15 ml) was added to $Na(CN)BH_3$ (500 mg). The mixture was stirred for 65 h at room temperature. The reaction was concentrated in vacuo and taken up in 2N aqueous NaOH (20 ml) and extracted with ethyl acetate (150ml). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by medium pressure liquid chromatography using a gradient solvent system of 2:98 methanol/methylene chloride followed by 0.5:5:95 NH_4OH/methanol/methylene chloride to give 170 mg (49% yield) of the title compound as a clear oil. [^{1}H]-NMR ($CDCl_3$) consistent with structure.

EXAMPLE 12

(S)-1-(Pyridin-4-ylmethyl)-Piperidine-2-Carboxylic Acid (1,7-di-pyridin-3-yl)heptan-4-yl) ester



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Following the method described in Example 11, mixture of the amine (300 mg, 0.79 mmol) from Example 10, part B and 4-pyridinecarboxaldehyde (0.5 g, 4.67 mmol) in methanol (15 ml) was added to $Na(CN)BH_3$ (500 mg). The mixture was stirred for 65 h at room temperature. The reaction was concentrated in vacuo and taken up in 2N aqueous NaOH (20 ml) and extracted with ethyl acetate (150ml). The organic layer was dried over $MgSO_4$, concentrated in vacuo and purified by medium pressure liquid chromatography using a gradient solvent system of 2:98 methanol/methylene chloride followed by 0.5:5:95 NH_4OH/methanol/methylene chloride to give 70 mg (19% yield) of the title compound as a clear oil. [^{1}H]-NMR ($CDCl_3$) consistent with structure.